REMARKS

Applicants and their undersigned representative wish to thank Supervisory Primary Examiner Sreeni Padmanabhan and Examiner San-ming Hui for their time and the courtesies they extended to applicants and the undersigned during the November 18 telephonic interview. It is believed that this discussion was very helpful in considering the issues in this application.

As a result of the interview, claim 37 is amended, and claims 38-41 are added. Neither change was requested nor required by the Examiners; however, it is believed that the amendments to claim 37 will be helpful to the consideration of the case, and claims 38-41 will assist in examination.

There was extensive discussion of the Huber reference. It is believed that there was agreement that Huber states:

> "of the esters of alcohols having 4-8 carbon atoms, I prefer to use n-hexyl nicotinate. The hexyl ester is the most effective of the group and in therapeutic concentrations it is substantially free of undesired side effects."

(Emphasis added) It is believed that it was further agreed that, at Column 2, line 52, a 10% solution of n-hexyl nicotinate is taught, and at column 3, lines 4-5, it is taught that the vasodilation effect ceased after 2 hours. Yet further, at column 3, lines 17-18, 5% solutions of n-hexyl and n-hexyl nicotinate are taught with a vasodilation effect of 2-3 hours (column 3, line 25). Further, a formulation of n-octyl nicotinate is described at column 4, lines 41-50, but no properties are attributed thereto.

It is submitted that, given Huber's statements regarding n-hexyl nicotinate, one must conclude that Huber did not see, teach, or envision n-octyl nicotinate as being as effective as the n-hexyl compound.

With this in mind, it is noted that a 10% solution of n-hexyl nicotinate was said to have a vasodilatory effect of 2 hours, and one of 5%, 2-3 hours.

Applicants, however, tested n-octyl, nicotinate at 0.1% - 1/50th of the weakest solution of Huber. As table 2 shows, the vasodilatory effect lasted for 4-6 hours. In other words a formulation, 1/50th of the strength of the prior art, was more effective in oxygen delivery.

Nothing in Huber would lead the artisan to believe this would be the case. As was pointed out, Huber says explicitly that the hexyl compound is best.

With respect to the Examiner's position that the duration of the C8 compound's effects were expected, the following is noted. First, the Examiner has argued that larger compounds take more time to diffuse into cells.

While this may be the case, a longer diffusion time does not mean a longer therapeutic effect. Vasodilation is the effect desired, i.e., enhanced delivery of oxygen. Applicants show, in Table 1 at page 6, that compounds with an alkyl group larger than 12 carbons do not have a vasodilatory effect, even though it must be presumed that they partition into skin more slowly than the C8 compound. The speed of partition is not linked to the vasodilatory effect. If it were, the larger the compound, the better it would function. Such is not the case. In other words, for compounds of C12 or bigger, the duration of the effect is zero, because there is none. Hence, a nexus is not made out.

Second, as has been pointed out previously, and during the interview, it cannot be said that the smaller the molecule, the longer the effect. If this were the case, C6 would have a longer effect than C8, C4 would have a longer effect than C6, and so forth. As Table 2 at page 6 – and the Huber reference – show, however, is that this is not the case either.

The fact is the claimed range of C8-C10 is neither suggested by Huber – which says nothing about larger molecules – nor are the properties shown in Tables 1 and 2 suggested thereby.

Otsuka does not remedy these failings. As was pointed out at the interview, this reference does not discuss nicotinic acid compounds at all. Further, it teaches that butyl benzoate is used to expedite the delivery of drugs through the skin. In contrast, as the specification shows, when butyl benzoate is used in combination with the described nicotinic acid alkyl esters. The role of the butyl benzoate is to "scavenge" digestive enzymes, so that more of the C8-C10 alkyl esters can get to the cells, and then be converted to the active drug, nicotinic acid.

It is "black letter law" that a reference which teaches an effect for a compound not claimed, does not provide a useful basis for a prior art rejection. The combination of Huber and Otsuka does not make out a prima facie case.

Withdrawal of the rejection, and allowance of claims 30-41 are believed proper and urged.

Respectfully submitted,

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